REMARKS

Pending Claims

As an initial matter, the undersigned gratefully acknowledges courtesies extended by the Examiner during an interview conducted on March 29, 2005 (hereinafter "interview"). The Examiner's suggestions regarding the claims have been helpful.

Unless specified otherwise, the terms "Action" or "Office Action" shall refer to the Final Office Action dated October 19, 2004.

Applicant requests that the Reply dated February 22, 2005 not be entered into the record in favor of the present submission.

Claims 1-25 were previously canceled in favor of pending claims 25-30. Claims 26-28 have been withdrawn from consideration. However, the Office indicated that claims 26-28 would be rejoined once there was allowable subject matter. It is believed that claims 25 and 29-30 are in condition for allowance. Rejoinder of claims 26-28 is hereby respectfully requested in line with paragraph 2 of the Action at pg. 2.

Claim 25 has been amended to make what was implicit more precise. Specifically, the claim has been amended to specify that the method selected calcification condition status, namely a lower peak bone mass. Support can be found throughout the disclosure including the claims as filed originally. For instance, see pg. 5, lines 24-30; and claim 2 as filed originally, for instance.

Claim 25 has been further amended to remove recitation of the reference to Genbank Accession No. L24756. Instead, the featured bone sialoprotein gene promoter is referenced as

"SEQ ID NO. 25" throughout the body of the claim. The change has been made at the request of the Examiner. See pg. 6, first full paragraph. Further support can be found in the Declaration of Dr. Kusk filed August 3, 2004. In that Declaration Dr. Kusk stated, among other things, the chemical identity of the list of sequences referred to by Genbank Accession Nos. L24756, M55270, D14813 and AB008821 and that those sequences were available to others well before the priority date of the instant application. Decl. at ¶¶ 6-7 and the prior response. Each of the L24756, M55270, D14813 and AB008821 sequences referenced by Dr. Kusk has been assigned identifiers as SEQ ID Nos. 25, 26, 27 and 28, respectively. Further support can be found throughout the instant application in which each of the Genbank reference numbers are recited multiple times.

Claim 25 has been further amended to point out more clearly relationship between a particular allelic variation (A=>G) and predisposition to a lower peak bone mass. Support for the amendment can be found throughout the application including the Drawings. Related amendments have been made to other independent claims.

Although claims 26-28 have been withdrawn by the Office, the present submission amends those claims to replace Genbank references with appropriate sequence identifiers. It is believed that amendment at this time is appropriate in the event the Examiner rejoins the claims. The amendment is in line with what has been requested by the Office for claim 25.

Pending claim 29 (as well as withdrawn claims 27 and 28) have been amended to depend further from claim 26. Particular support can be found, for example, at pg. 5, lines 16-23; pg. 6, lines 9-14; and pg. 7, lines 7- 20 (generally providing for methods involving "all four or any combination of two or more" promoters). Additional support can be found at pg. 32, lines 7-10 (disclosing, for instance, combination of the BSP and OPN promoters in a particular method); pg. 33, lines 7-11 (disclosing, for instance, combination of the MGP and OPN promoters in a particular method); and pg. 37, lines 12-16 (disclosing, for instance, combination of OPG and BSP promoters in a particular method). See also the data presented in Tables 3 and 4 for further

support.

New claim 32 finds particular support at pg. 37 through pg. 38, line 18 (disclosing the particular combination embodiment of the claim).

New claims 33-34 and 36-37 find specific support at pg. 9, line 14 to pg. 10, line 2.

New claim 35 is written with all of the language from claims 25-27.

Further support for the amendments and new claims can be found throughout the specification including the Drawings and claims as filed originally. No new matter has been added.

Applicant now turns to comments made by the Examiner in the Action as well as the Advisory Action (and interview) as follows.

FINAL OFFICE ACTION

Sequence Listing

Turning to paragraph 3 of the Action, the present submission includes a revised sequence listing that is in full compliance with the rules. It is noted that SEQ ID Nos. 25-28 have been added to that submission. However, it is not believed that SEQ ID Nos. 25-28 are "new matter". For instance, the Office has accepted that addition of the sequences is appropriate in view of Dr. Kusk's Declaration and the prior response. Moreover, the Examiner specifically requested the addition of the sequence identifiers in the prior Office Action. See pg. 6 of the prior Action, for instance. This submission is in compliance with that request.

The submission of the attached sequence listing is supported by a statement in accord

with 37 CFR §§ 1.821-1.825.

No new matter has been added by virtue of the claim amendments or sequence listing submission.

35 USC §112, first paragraph

Turning to the Action, claims 25, 29 and 30 stand rejected under 35 USC §112, first paragraph, as containing new subject matter. While Applicant respectfully disagrees, basis for the rejection has been addressed by this submission. For instance, the term "BSP II" has been removed. Thus, the rejection as stated is moot. Reconsideration and withdrawal are respectfully requested.

35 USC §112, second paragraph

Claims 25, 29 and 30 stand rejected under 35 USC §112, second paragraph as being indefinite on various grounds. While Applicant must respectfully disagree that the claims are at all indefinite, basis for the rejection has been fully addressed.

For instance, the phrase "selected calcification status" has been specified by reciting "lower bone peak mass". Insertion of the phrase helps bring the beginning of claim 25 more into conformity with its end.

At pg. 4 of the Action, last paragraph, the Office found the phrase "lower peak bone mass" indefinite. Applicant respectfully disagrees for the following reasons.

It would be clear to a worker reading Applicant's specification that the term "lower" in Claim 25 refers to an individual being predicted to be likely to have a lower peak bone mass than

would be average for a population of like individuals of unknown allelic variation status. This is in accordance with what is described and exemplified in the specification, particularly from page 27 onwards where the relevant allelic variations were matched against peak bone mass for healthy women participating in an eighteen year study. From this it was observed that the variant sequence of Claim 25 containing adenine at position 1496 and also the presence of guanine at position 1869 were associated with a lower than average peak bone mass in this group. That meaning would be clear and unambiguous. Clearly, where Claim 25 associates A at 1496 bp with a predisposition to lower peak bone mass it is indicating that the peak bone mass will be low by comparison with individuals with G but an average population will have a mixture of both A and G, so an individual with A would be expected to have a relatively low peak bone mass as against the average also.

However to advance prosecution, Applicant has amended claim 25 to make relationship between the featured allelic variation and predisposition to lower peak bone mass even clearer. In particular, the claim now reads that when the specified adenine variation is present within the promoter sequence, the individual will have a predisposition to lower peak bone mass than when guanine is present.

In view thereof, Applicant respectfully requests reconsideration and withdrawal of the rejection.

35 USC §112, first paragraph

Claims 25, 29 and 30 stand rejected as not being enabled. While Applicant disagrees with the rejection, basis for it has been addressed. In particular, the suggestion made by the Examiner at pg. 6, first full paragraph has been adopted ie., the reference to the GenBank record has been deleted in favor of a sequence identifier (SEQ ID NO. 25).

Claims 25, 26 and 30 were further rejected on grounds of non-enablement at pgs. 6-7 of

the Action, bridging paragraph. While Applicant respectfully disagrees with the stated basis for rejecting these claims on pgs. 6-11, grounds for the rejection have been addressed. Specifically, the phrase "selected calcification status" although not indefinite at all to one working in this field, has been made more clearly by adding "lower peak bone mass" to the claims.

Reconsideration and withdrawal of the rejection are requested.

ADVISORY ACTION AND INTERVIEW

Turning to the Advisory Action (dated March 14, 2005), the Office indicated at ¶3 that the instant amendment of claim 25 would raise a new issue under 112, second because it was allegedly not clear if the recitation of (SEQ ID NO: 25) as shown on the third line of the claim is a positive limitation or if it is an optimal limitation. Applicants believe the language "(SEQ ID NO: 25)" makes it abundantly clear that the recited promoter of the bone sialoprotein gene has the sequence set forth in the referenced sequence. The language would be particularly clear to one working in this field in view of the instant amendment to the specification at pg. 6, line 15 to pg. 7 through line 20.

During the interview, the undersigned understood the Examiner to take the position that claims 26-28 lacked sufficient support for the following language in claim 26 (as well as corresponding language in claims 27 and 28):

> associating the presence of said adenine in said sequence with a predisposition to a higher rate of loss of bone mass than when cytosine is present.

In response, Applicants respectfully submit that the language is fully supported by the specification and Drawings as filed originally.

For instance, and beginning with the language of claim 26 specifically, this relates of course to variations in the promoter of the matrix gla protein (MGP) gene. Page 9, line 3, stated

that the presence of A rather than C at position 242 is associated with a higher rate of bone mass loss. There is explicit basis for the claim language there. The physical steps needed for making the determination of which version of the promoter a person has would involve nothing that necessitates anything further by way of technical teaching to enable the skilled worker to make the determination. Respectfully, there is no basis for an allegation that there is a lack of enablement.

The next three paragraphs on page 9 (i.e. lines 5-10) provide equally exact basis for the similar language appearing at the end of claims 27 and 28 in relation to the osteopontin (OPN) gene promoter and the osteoprotegerin gene promoter (OPG/OCIF).

The language enjoys further support in Figure 5. It shows the results of comparing BMC (Bone Mineral Content) for the two versions of the MGP gene promoter referred to in claim 26. Demonstrably, the homozygous ZZ curve lies above the heterozygous curve. This showed that the presence of homozygous wild type C (see Figure 1 B for the wild type sequence) shows an initially higher BMC and that the heterozygous curve falls away from this with time, thus showing a higher rate of bone loss where C is substituted by A. Thus, the effect specified in claim 26 is demonstrated.

The corresponding langauge in claim 27 finds similar support in the application as filed.

There are multiple grounds for supporting this claim throughout the specification. The first is illustrated in Figure 6 where the wild type (G containing) homozygous or heterozygous group is shown to retain its BMC value better over time than the homozygous adenine containing group (curve bb). This demonstrates that the presence of adenine is associated with a faster rate of loss of bone mass, even where the initial absolute values were the same.

An additional ground is illustrated in Figure 8 where the homozygous wild type thymine containing homozygous population has a lower bone mass than the heterozygous or homozygous cytosine containing population.

The additive character of the predispositions indicated by the OPN variants of Claim 27 and the BSP variants of claim 25 is illustrated and discussed on page 33 with reference to Figure 9.

The corresponding langauge in claim 28 finds similar support in the application as filed.

For instance, particular support is shown in Figure 11 where the population containing at least one non-wild type guanine (see Figure 10 for the wild type sequence) has a lower bone mass than the homozygous wild type population with adenine.

The additive character of the predispositions indicated by the OPG variants of Claim 28 and the BSP variants of claim 25 is illustrated and discussed on page 39 with reference to Figure12.

Thus not only is the application explicit in providing literal basis for the claim language, but the working of the invention is demonstrated.

In view thereof, it is respectfully submitted that all concerns raised in the Advisory Action and interview have been addressed.

CONCLUSION

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. Applicant's representative would like to discuss this case with the Examiner to learn if any outstanding issues remain after consideration of this submission. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Although it is not believed that any further fee is needed to consider this submission, the Office is hereby authorized to charge our deposit account **04-1105** should such fee be deemed necessary.

Respectfully submitted,

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